

Docket No.: 0649-1380PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazutaka IKEDA et al.

Application No.: 10/594,597

Confirmation No.: 6839

Filed: September 28, 2006

Art Unit: 1634

For: METHOD OF EVALUATING DRUG
SENSITIVITY BY ANALYZING THE MU-
OPIOID RECEPTOR GENE

Examiner: S. T. Kapushoc

SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madame:

I, Kazutaka IKEDA, do declare and state as follows:

1. I am a co-inventor of the instant application.
2. My *curriculum vitae* was provided with the Declaration, which was executed on November 15, 2009, and submitted to the United States Patent and Trademark Office on November 16, 2009.
3. In further response to the Examiner's allegation that the present application fails to enable the instant claims, submitted herein below are additional data, which further supports my opinion that the polymorphisms described in the present claims are reliably associated with a sensitivity to drugs.
4. My opinion regarding the reliability of the association, as set forth in the November 16, 2009, Declaration, was based, in part, on the teachings in the present application, which describe

that the polymorphism at position IVS3+A6151G, as specified in the present claims, is associated with methamphetamine sensitivity at a significant value of $p = 0.0269$, *see* Table 10, page 59, of the originally filed application.

5. In addition, I noted that Table 6 of the present application, as amended on November 16, 2009, describes that IVS3+A6151G is in strong linkage disequilibrium with IVS3+A8449G, *i.e.*, $D' = 1.000$ and $r^2 = 0.800$. Accordingly, an ordinary artisan would have recognized that IVS3+A8449G is also associated with drug sensitivity.

6. In further support of my opinion, I submitted data that confirmed the association of IVS3+A8449G with drug sensitivity, *i.e.*, fentanyl. Specifically, the previously submitted data demonstrated an association between IVS3+A8449G and 24 hour postoperative fentanyl use.

7. Submitted herein below is data that confirms that IVS3+A6151G is not only associated with methamphetamine use, but is also associated with 24 hour postoperative fentanyl use.

Table 2'

Patients' demographic and clinical data

	All patients		IVS3+A8449G (rs9384179)		IVS3+A6151G (rs598682)	
			AA	AG+GG	GG	GA+AA
Age (years)	25.8±7.4	(15-50)	25.9±7.4	25.5±8.1	26.0±7.5	24.7±7.2
Male/Female	97/183		71/148	26/35	79/161	18/22
Body weight (kg)	57.9±11.1	(38-128)	57.2±10.8	60.5±11.8	57.6±10.9	60.0±12.3
Total propofol dose (mg/kg)	25.0 [22.0, 27.9]	(5-42)	25.0 [22.0, 27.8]	25.5 [22.5, 28.7]	25.0 [22.0, 28.0]	25.2 [22.3, 27.2]
Preoperative fentanyl use (µg/kg)	2		2	2	2	2
Intraoperative fentanyl use (µg/kg)	3.9 [2.9, 5.3]	(0-13.6)	3.9 [2.9, 5.2]	3.8 [3.0, 5.6]	3.9 [2.9, 5.2]	3.9 [3.0, 5.5]
24-h postoperative fentanyl use (µg/kg)	2.3 [1.1, 4.1]	(0-13.8)	2.5 [1.3, 4.3]	1.5 [0.8, 3.4]*	2.3 [1.3, 4.2]	1.4 [0.6, 3.0]*
Perioperative fentanyl use (µg/kg)	6.6 [5.0, 8.6]	(0.8-24.0)	6.7 [5.2, 8.6]	6.0 [4.6, 8.3]*	6.6 [5.1, 8.6]	5.8 [4.5, 8.0]*
Total perioperative analgesic use (µg/kg)	7.5 [5.9, 9.5]	(1.8-25.3)	7.6 [6.1, 9.6]	6.9 [5.4, 8.9]*	7.6 [6.0, 9.6]	6.7 [5.4, 9.0]*
VAS pain score at 3 h (mm)	25 [13, 48]	(0-90)	26 [13.5, 50]	24 [10, 36]	25 [13, 49]	25 [14, 42]
VAS pain score at 24 h (mm)	25 [10, 40.5]	(0-83)	25 [10, 44.5]	25 [8, 36]	25 [10, 42]	25 [9, 38]

Data are expressed as numbers, mean ± SD (range), or median [interquartile range].

(*) p < 0.1, compared with subjects not carrying minor allele.

* p < 0.05, compared with subjects not carrying minor allele.

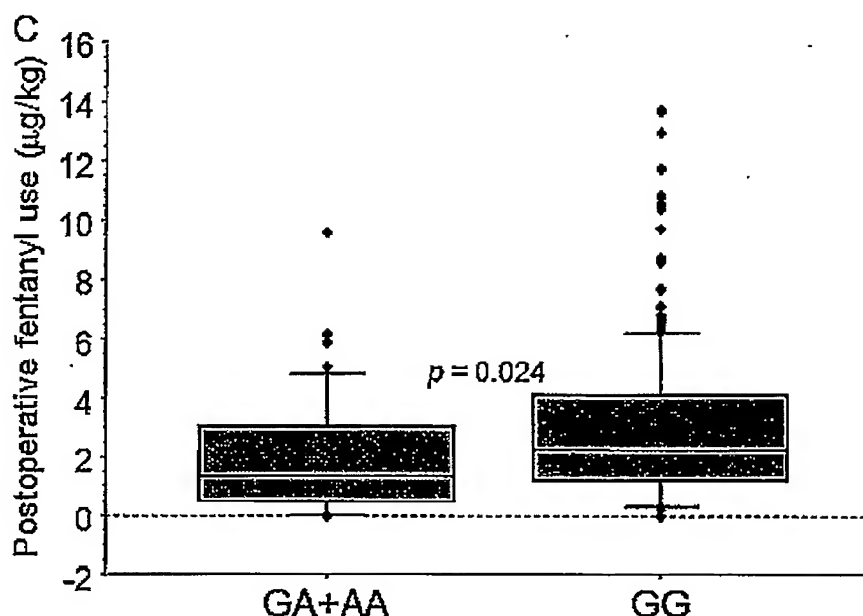


Fig. 3. Associations between genotypes of the IVS3+A6151G SNP (GG, n = 240; GA + AA, n = 40) and (C) 24-h postoperative fentanyl use. Data are expressed by box and whisker plots. Upper and lower ends of boxes represent the 75th and 25th percentiles. Whiskers represent the 90th and 10th percentiles, and filled circles represent outliers. The median is depicted by a solid line in the box.

8. Accordingly, an ordinary artisan would have recognized from the data described in the November 16, 2009, Declaration and the instant Declaration that IVS3+A844G, (rs9384179), is associated 24 hour postoperative fentanyl use, *i.e.*, $p = 0.010$, and that IVS3+A6151G, (rs598682), is also associated with 24 hour postoperative fentanyl use, *i.e.*, $p = 0.024$.

9. In view of the foregoing and the information provided in the November 16, 2009, Declaration, it is my opinion that an ordinary artisan would have recognized from the instant application that there is a predictable association between drug sensitivity and the gene polymorphisms described in the present claims.

STATEMENT UNDER 18 U.S.C. § 1001

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: Kazutaka Ikeda
Kazutaka Ikeda

Date: November 26, 2009